the human or animal with a disease of the eye with a composition comprising an effective angiogenesis-inhibiting amount of 2-methoxyestradiol.

41. (Once Amended) The method of Claim 40, wherein the complications of the female reproductive system are associated with ovulation, implantation of a blastula, menstruation, or menopause.

REMARKS

Claims 26-42 are pending in the present application, and all claims were rejected in the May 30, 2002 Office Action. By this Amendment and Response, the specification and Claims 32, 34, and 41 are amended. Applicants respectfully request reconsideration of the present claims in view of these foregoing amendments and the following remarks.

OBJECTION TO THE SPECIFICATION

According to the May 30, 2002, Office Action, the amendment filed May 23, 2002, is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. The purported new matter consists of entries in Table 1 for a) all nerve cell diseases; b) all diseases of the eye; c) all female reproductive system complications from undesired angiogenesis; d) all tumors; and e) osteoporosis.

By the amendments entered above, the entries in Table 1 directed to "nerve cell diseases" and "diseases of the eye" are amended to recite, "nerve cell diseases characterized by undesirable angiogenesis" and "diseases of the eye characterized by undesirable angiogenesis." The publications associated with these table entries are directed to defining the role of **angiogenesis** in that disease state (*see* heading to column 2 of Table 1). Applicants note the entry for "female reproductive system complications" in Table 1 already features only those complications resulting "...from undesired angiogenesis." Further, Applicants note what is also well-known to those skilled in the art and already available to the public, is that "tumors" and "osteoporosis" are also characterized by undesirable angiogenesis, as described in the citations corresponding to these table entries.

The specification discloses that "cell mitosis is important for...angiogenesis and angiogenesis related diseases" (page 2, lines 20-23). Because 2-methoxyestradiol inhibits cell mitosis (see, for example, page 2, lines 11-12; page 2, lines 25-28; page 13, Table 2; page 11, Example 1), it also treats any disease characterized by undesirable angiogenesis or any angiogenesis-related disease. The specification (page 6, lines 25-26; page 3, lines 7-8) and Table 1 provide a non-exclusive list of *exemplary* mammalian diseases characterized by undesirable angiogenesis that can be treated with 2-methoxyestradiol. According to the specification, such diseases "include *but are not limited to*..." those incorporated into the list of diseases provided (page 3, lines 6-7; emphasis added).

Applicants respectfully submit that the application as filed necessarily encompasses all nerve cell diseases *from undesired angiogenesis*, all diseases of the eye *from*

undesired angiogenesis, all female reproductive system complications from undesired angiogenesis; all tumors, and osteoporosis, because each of these diseases and complications arises from undesired angiogenesis and is characterized by abnormal cell mitosis. The specification need not disclose what is well-known to those skilled in the art and already available to the public. *In re Buchner,* 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991).

Therefore, Applicants respectfully submit that, in view of the amendments entered above, no new matter has been added to the application. Accordingly, Applicants respectfully request removal of the "new matter" objection under 35 U.S.C. § 132.

CLAIM REJECTIONS

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 27, 32, 34, and 40-42 were rejected in the May 30, 2002 Office Action under 35 U.S.C. § 112, first paragraph, because it is the Examiner's view that these claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art to which it pertains that Applicants had possession of the claimed invention. The Examiner appears to base this rejection on the fact that some of the diseases and conditions recited in the rejected claims are not specifically recited in the specification. Applicants respectfully traverse this rejection because the specification provides support for Claims 27 and 40-42 as written, and for Claims 32 and 34 as amended, as follows.

The specification clearly discloses that "cell mitosis is important for...angiogenesis and angiogenesis related diseases" (page 2, lines 20-23). Because 2-methoxyestradiol inhibits cell mitosis (see, for example, page 2, lines 11-12; page 2, lines 25-28; page 13,Table 2; page 11, Example 1), it also treats any disease characterized by undesirable angiogenesis or any angiogenesis-related disease. The specification (page 6, lines 25-26; page 3, lines 7-8) and Table 2 provide a non-exclusive list of *exemplary* mammalian diseases characterized by undesirable angiogenesis that can be treated with 2-methoxyestradiol. According to the specification as filed, such diseases "include *but are not limited to*..." those incorporated into the list of diseases provided (page 3, lines 6-7; emphasis added).

Importantly, Applicants submit that the present application as filed necessarily encompasses *all* specific, non-recited diseases characterized by undesired angiogenesis that were know in the art. Applicants maintain that the specification conveys to one skilled in the art, that Applicants, as of the filing date, were in possession of the claimed invention. It is well known that "[t]he invention claimed does not have to be described in 'ipsis verbis' in order to satisfy the description requirement of § 112." *In re Lukach,* 442 F.2d 967, 969 (C.C.P.A. 1971)). The specification need not disclose what is well-known to those skilled in the art and already available to the public. *In re Buchner,* 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991).

Thus, Claim 27 (tumors), amended Claim 32 (nerve cell diseases characterized by undesirable angiogenesis), amended Claim 34 (diseases of the eye characterized by

undesirable angiogenesis), Claims 40 and 41 (undesired angiogenesis associated with complications arising from the female reproductive system), and Claim 42 (osteoporosis) are all drawn to methods of treating the specified diseases or conditions by administering a composition comprising 2-methoxyestradiol. What is well-known to those skilled in the art and already available to the public, is that *each* of these diseases and conditions is characterized by undesirable angiogenesis, and is therefore encompassed by the present invention. References that disclose the role of angiogenesis in each disease or condition generally are found in Table 1.

Accordingly, the subject matter of Claims 27, 32, 34, and 40-42 is described in the specification in a way as to reasonably convey to one skilled in the art to which it pertains that Applicants had possession of the claimed invention. Therefore, Applicants respectfully request removal of the rejection under 35 U.S.C. § 112, first paragraph, and allowance of these claims.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 41 was rejected in the May 30, 2002 Office Action under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. This rejection is based upon the improper dependency of this claim.

By this amendment, Claim 41 is amended to depend from Claim 40, rather than from Claim 30, thereby obviating this rejection under 35 U.S.C. § 112, second

paragraph. Therefore, Applicants respectfully maintain that Claim 41 is definite within the meaning of 35 U.S.C. § 112, second paragraph, and request withdrawal of this rejection.

Provisional, Obviousness-Type Double Patenting Rejection

Claims 26-42 are subject to a provisional, obviousness-type double patenting rejection in view of Claims 15 and 19 of co-pending U.S. Application No. 09/899,702. It is the Examiner's position that the conflicting claims cited are both drawn to methods of treating angiogenesis-related diseases using 2-methoxyestradiol and Claim 19 of Application No. 09/899,702 recites the use of 2-ethoxyestradiol. Applicants note this provisional rejection and will address it when Application No. 09/899,702 issues, and the provisional nature of the rejection is removed.

Claim Rejection under Obviousness-Type Double Patenting

Claims 26-42 are subject to obviousness-type double patenting rejections in view of Claims 1 and 2 of U.S. Patent No. 5,504,074 and Claims 1 and 6 of U.S. Patent No. 5,661,143. Claims 27-28 are also subject to an obviousness-type double patenting rejection in view of Claims 1-3 of U.S. Patent No. 5,643,900. It is the Examiner's position that, although the conflicting claims are not identical, they are not patentably distinct because they are both drawn to a method of treating angiogenesis-related diseases using 2-methoxyestradiol.

Further, the Examiner states that Claim 6 of U.S. Patent 5,661,143 recites the use of 2-ethoxyestradiol. Applicants respectfully traverse these rejections and maintain that these claims are patentably distinct. For example, there is no *a priori* reason that would lead one to expect that 2-ethoxyestradiol and 2-methoxyestradiol would both exhibit similar physiological behavior, in view of the differences in their molecular size, shape, weight, hydrogen-bonding capability, polarity, dielectric constant, solubility, and the like.

However, in the interest of advancing the prosecution of this application, Applicants submit herewith a terminal disclaimer under 37 C.F.R. § 1.321(c) disclaiming an extension of the patent term, if any, of the present invention beyond the patent terms of the above-referenced patents in order to expedite allowance of the present claims. Accordingly, Applicants respectfully request withdrawal of all the above obviousness-type double patenting rejections, and allowance of Claims 26-42.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

In accordance with 37 CFR 1.121(b), the following replacement paragraph shows all the changes made by the foregoing amendment relative to the previous version of the paragraph. (The following paragraph was added in the Second Preliminary Amendment (filed May 23, 2002), to the specification, page 7, immediately after line 4, and before the section entitled "Improved Estradiol Derivative Synthesis".)

Table 1 provides a number of sample references which correlate the role of angiogenesis in numerous disease states.

Table 1

Disease State	**Publication defining role of angiogenesis in disease state**
atherosclerosis	PCT International Publication Number WO91/10424, Published July 25, 1991; Kahlon et al, *Angiogenesis in Atherosclerosis* Can. J. Cardio. (1992) (abstract)
Tumors	Moulton, K.S. Et al. *Angiogenesis in the huPBL-SCID Model of Human Transplant Rejection.* Transplantation Vol. 67 No. 12 Jun 1999 pp.1626-1631 (see page 1630, col. 2, lines 1-2 of the second paragraph); European Application Number 89100714.8, Published July 26, 1989.
solid tumors	PCT International Publication Number WO91/10424, Published July 25, 1991

benign tumors	Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography.* Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 469, abstract)
metastatic tumors	Mahadevan, V. Et al. *Metastasis and Angiogenesis.* Acta Oncolgica Vol. 29 No. 1 1990 pp. 97-103 (page 97, abstract)
hemangiomias	PCT International Publication Number WO91/10424, Published July 25, 1991
nerve cell diseases characterized by undesirable angiogenesis	Siedlak, S.K. Et al. *Basic Fibroblast Growth Factor Binding Is a Marker for Extracellular Neurofibrillary Tangles in Alzheimer Disease.* The Journal of Histochemistry and Cytochemistry: Official Journal of the Histochemistry Society Vol. 37 No. 7 July 1991 pp. 899-904.
acoustic neuroma or neurofibroma	Eldridge, R. *Central Neurofibromatosis with Bilateral Acoustic Neuroma.* Advances in Neurology Vol. 29 1981 pp. 57-65 (page 62-63, each paragraph)
diseases of the eye characterized by undesirable angiogenesis	See those listed for claim 65, as well as those on the copy of the attached chart filed for a related patent application 09/126,542 (copies of those references not attached)
retinopathy of prematurity	Penn, J.S. Et al. *Variable Oxygen Exposure Causes Preretinal Neovascularization in the Newborn Rat.* Investigative Ophthalmology & Visual Science Vol. 34 No. 3 Mar. 1993 pp. 576-585 (page 584, col. 2, final paragraph)
diabetic retinopathy	PCT International Publication Number WO91/10424, Published July 25, 1991
corneal graft rejection	Cursiefen, C. Et al. *Angiogenesis in Corneal Diseases: Histopathologic Evaluation of 254 Human Corneal Buttons with Neovascularization.* Cornea Vol. 17 No. 6 Nov. 1998 pp. 611-613

neovascular glaucoma	PCT International Publication Number WO91/10424, Published July 25, 1991
retrolental fibroplasias	PCT International Publication Number WO91/10424, Published July 25, 1991.
Trachoma	European Application Number 89100714.8, Published July 26, 1989
Degeneration	Penfold et al., *Age-related macular degeneration: ultrastructural studies of the relationship of leucocytes to angiogenesis*, Graefes Arch Clin Exp Ophthalmol 1987; 225(1):70-6 (abstract)
inflammation	Moulton, K.S. Et al. *Angiogenesis in the huPBL-SCID Model of Human Transplant Rejection.* Transplantation Vol. 67 No. 12 Jun 1999 pp.1626-1631 (page 1626,col. 1, line 1)
pyogenic granulomas	Almeida, B.M. Et al. *The Distribution of LH39 Basement Membrane Epitope in the Tumour Stroma of Oral Squamous Cell Carcinomas.* The Journal of Pathology Vol. 166 No. 4 Apr. 1992 pp. 369-374 (page 369, last four lines of Summary); European Application Number 89100714.8, Published July 26, 1989
vascular malfunctions	Arnold, F. Et al. *Angiogenesis in Wound Healing.* Pharmacology & Therapeutics Vol. 52 No. 3 Dec. 1991 pp. 407-422; Poole, T.J. Et al. *Developmental Angiogenesi: Quail Embryonic Vasculature.* Scanning Micrscopy Vol. 2 No. 1 Mar. 1998 pp. 443-448; European Application Number 89100714.8, Published July 26, 1989
abnormal wound healing	Arnold, F. Et al. *Angiogenesis in Wound Healing.* Pharmacology & Therapeutics Vol. 52 No. 3 Dec. 1991 pp. 407-422 (page 407, col. 2, line 1 of the second paragraph; page 412, section 2.4.5 "Negative Controls on Angiogenesis;" page 416, section 3.4 "Overhealing")
inflammatory disorders	Locci, M. Et al. *Angiogenesis: A New Diagnostic*

	Aspect of Obstetric and Gynecologic Echography. Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 453, second column, line 8)
Gout, gouty arthritis	three articles showing that factors inducing gout are IL-1, 2, and 6: Hashizume, K. Et al. *A Role of Interleukin-1 (IL-1) in Crystal-Induced Arthritis.* Advances in Experimental Medicine and Biology Vol. 253A 1989 pp. 219-224; Campen, D.H. Et al. *Serum Levels of Interleukin-2 Receptor and Activity of Rheumatic Diseases Characterized by Immune System Activation.* Arthritis and Rheumatism Vol. 31 No. 11 Nov. 1988 pp. 1358-1364; Brozik, M. Et. Al. *Interleukin 6Levels in Synovial Fluids of Patients with Different Arthritides: Correlation with Local IgM Rheumatoid Factor and Systemic Acute Phase Protein Production.* The Journal of Rheumatology Vol. 19 No. 1 Jan. 1992 pp. 63-68; and five articles showing that IL-1, 2, 4, 6 and 8 stimulate angiogenesis: Fan, T.P. Et al. *Stimulation of Angiogenesis by Substance P and Interleukin-1 in the Rat and its Inhibition by NK_1 or Interleukin-1 receptor antagonists.* British Journal of Pharmacology Vol. 110 No. 1 Sept. 1993 pp. 43-49; Cozzolino, F. Et al. *Interferon-alpha and Interleukin 2 Synergistically Enhance Basic Fibroblast Growth Factor Synthesis and induce Release, Promoting Endothelial Cell Growth.* The Journal of Clinical Investigation Vol.91 No. 6 Jun 1993 pp.2504-2512; Wojta, J. Et al. *Interleukin-4 Stimulates Expression of Urokinase-Type-Plasminogen Activator in Cultured Human Foreskin Microvascular Endothelial Cells.* Blood Vol. 81 No. 12 June 15, 1993 pp. 3285-3292; Sun, W.H. Et al. *In Vivo and in vitro Characteristics of Interleukin 6-transfected B16 Melanoma Cells.* Cancer Research Vol. 52 No. 19 Oct. 1, 1992 pp. 5412-5415; Hu, D.E. Et al. *Interleukin-8 Stimulates Angiogenesis in Rats.* Inflammation Vol. 17 No. 2 Apr. 1993 pp. 135-143
rheumatoid arthritis	PCT International Publication Number WO91/10424, Published July 25, 1991

psoriasis	PCT International Publication Number WO91/10424, Published July 25, 1991
immune disorders	PCT International Publication Number WO91/10424, Published July 25, 1991
Behcet's Syndrome	Aydintug, A.O. et al. *Antibodies to Endothelial Cells in Patents with Behcet's Disease.* Clinical Immunology and Immunopathology Vol. 67 No. 2 May 1993 pp.157-162 (page 157, entire first col.; page 160, col. 2, second full paragraph)
Osler-Weber-Rendu disease	Burke et al., *Pulmonary arteriovenous malformation: a critical update.* Am. Rev. Respir. Dis. Vol 134(2) Aug 1986 334-9 (abstract); Van Cutsem et al., *Estrogen-progeserone treatment of Osler-Wever-Rendu disease.* J. Clin Gastroenterol Vol 10(6):676-9 Dec. 1988 (abstract)
Female Reproductive system complications from undesired angiogenesis	Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography.* Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 453, col. 1, line 25 to the end of col. 2); Logan, A. *Angiogenesis.* Lancet Vol. 341 No. 8858 Jun 1993 pp. 1467-1468 (page 1468, col. 1, first three full paragraphs)
Ovulation, implantation of a blastula, menstruation, menopause	Locci, M. Et al. *Angiogenesis: A New Diagnostic Aspect of Obstetric and Gynecologic Echography.* Journal of Perinatal Medicine Vol. 21 No. 6 1993 pp. 453-473 (page 453, col. 1, line 25 to the end of col. 2); Logan, A. *Angiogenesis.* Lancet Vol. 341 No. 8858 Jun 1993 pp. 1467-1468 (page 1468, col. 1, first three full paragraphs)
Osteoporosis	Schaub et al, *Novel agents that promote bone regeneration*, Curr Opin Biotechnol, 1991 Dec; 2(6):868-71 (abstract)

In the Claims

In accordance with 37 C.F.R. § 1.121(c), the following version of the rewritten claims by the foregoing amendment shows all the changes made relative to the previous version of the claims.

32. (Once Amended) A method for treating nerve cell diseases characterized by undesirable angiogenesis in a human or animal comprising administering to the human or animal with the nerve cell disease a composition comprising an effective angiogenesis-inhibiting amount of 2-methoxyestradiol.

34. (Once Amended) A method for treating diseases of the eye characterized by undesirable angiogenesis in a human or animal comprising administering to the human or animal with a disease of the eye with a composition comprising an effective angiogenesis-inhibiting amount of 2-methoxyestradiol.

41. (Once Amended) The method of Claim [30] 40, wherein the [problems] complications of the female reproductive system are associated with ovulation, implantation of a blastula, menstruation, or menopause.

Conclusion

In view of the remarks and amendments entered above, Applicants submit that the claims define patentable subject matter and are in condition for allowance. A Notice of Allowance is therefore requested and such action is respectfully solicited.

If the Examiner believes any informalities remain in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is requested. No additional fees are believed due; however, the Commissioner is authorized to charge any deficiencies, or credit any overpayment to deposit account No. 11-0855.

Respectfully submitted,

By: David E. Wigley, Ph.D.
Reg. No. 52,362

Kilpatrick Stockton LLP
Suite 2800
1100 Peachtree Street
Atlanta, GA 30309-4530
Tel. 404.815.6500

Date: August 30, 2002
Our File: 05213-0493 (43170-253692)